Thirty-Day Readmission and Cost Analysis in Patients With Cirrhosis: A Nationwide Population-Based Data

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Accurate population-based data are needed on the rate, economic impact, and the long-term outcomes of readmission among patients with cirrhosis. To examine the rates, costs, and 1-year outcomes of patients readmitted within 30 days following their index hospitalization for complications of cirrhosis, we conducted a nationwide, population-based cohort study involving all patients with cirrhosis in Thailand from 2009 through 2013, using data from the National Health Security Office databases, which included those from nationwide hospitalizations. Readmission was captured from hospitals at all health care levels across the country within the Universal Coverage Scheme. For the 134,038 patients hospitalized with cirrhosis, the overall 30-day readmission rate was 17%. Common causes of readmission consisted of complications of portal hypertension (47%) and infections (17%). After adjusting for multiple covariates, predictors of 30-day readmission included hepatocellular carcinoma (odds ratio [OR] 1.95, 95% confidence interval [CI] 1.84-2.06), human immunodeficiency virus–related admission (OR 1.81, 95% CI 1.51-2.17) and cholangiocarcinoma (OR 1.64, 95% CI 1.3-2.05). In all, 2,936 deaths (13%) occurred during readmission, and an additional 14,425 deaths up to 1 year (63.5% total mortality among readmitted patients). Causes of death were mostly from liver-related mortality. Average cost at index admission for those with a 30-day readmission were significantly higher than those readmitted beyond 30 days or not readmitted. *Conclusions:* Patients hospitalized with cirrhosis complications had high rates of unscheduled 30-day readmission. Average hospitalization costs were high, and only 36.5% of patients readmitted within 30 days survived at 1 year. (*Hepatology Communications* 2020;4:453-460).

Cirrhosis is a leading cause of death worldwide, with an estimated increase from around 676,000 deaths in 1980 to over 1 million in 2010.[1] Liver cirrhosis is also associated with increased resource use. The overall health care costs of liver cirrhosis includes significantly high direct costs (medical treatment such as medicine and hospitalization costs) and indirect costs (loss of work productivity and reduced health-related quality of life), with estimated direct cost to be $2.5 billion and estimated indirect cost to be $10.6 billion in the United States.[2] Because cirrhosis is a progressive disorder and chronic disease, patients with decompensated cirrhosis often experience multi-organ failure with consequences including hepatic encephalopathy, infection, gastrointestinal hemorrhage, fluid

Abbreviations: CDI, Clostridium difficile infection; CI, confidence interval; CTP, Child-Turcotte-Pugh; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; HIV, human immunodeficiency virus; HR, hazard ratio; ICD-10, International Classification of Diseases and Related Health Problems, 10th Revision; IQR, interquartile change; IRB, institutional review board; MELD, Model for End-Stage Liver Disease; OR, odds ratio; SBP, spontaneous bacterial peritonitis; WHO, World Health Organization.

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overload, and frailty.[3,4] Because of their insubstantial condition, patients with decompensated cirrhosis are more frequently hospitalized and rapidly readmitted shortly after their discharge, and the pooled estimate of 30-day readmissions was reported at 26% (95% confidence interval [CI], 22%-30%).[5] These data were collected from a selection of patients from tertiary care centers, each limited by the possibility of uncounted readmissions to other hospitals and selected patients from referral centers.[6] Recently, Tapper et al.[7] reported on a population-based study of readmissions among patients who were admitted to hospitals in multiple states, demonstrating 30-day and 90-day rates of readmission of 12.9% and 21.2%, respectively. However, no nationwide multicenter data from population-based data outside the United States are presently available.

Thirty-day readmission rates are considered an indicator of hospital quality and performance measures. Readmissions also have huge impacts on the overall costs of health care. Repeated hospitalizations are harmful to patients and constitute a burden to caregivers and health care systems. The annual post-index hospitalization costs for those with a 30-day readmission were substantially higher than those readmitted beyond 30 days or those not readmitted.[4] Average annual costs concerning hospitalizations for chronic liver disease are around $2 billion.[8] Understanding and assessing the national trends in cirrhosis readmissions would provide the keys to success for any given intervention intending to reduce readmission rates for patients with cirrhosis. Therefore, in this study we examined incidence and risk factors for readmission of a nationwide cohort study of patients with cirrhosis who required readmission within 30 days.

Methods

DATA SOURCE AND PATIENT SELECTION

All patient-encountered data were obtained from the National Health Security Office. Data extracted from national inpatient databases from 2009 through 2013 were all-payer parties under the Thai Ministry of Public Health and representative administrative data sets totaling a population of 49.1 million. The databases included those from nationwide hospitalizations. The National Health Security Office database contained 28,294,685 individual discharge records from 2009 through 2013. By using the International Classification of Diseases, 10th Revision (ICD-10), Clinical Modification, diagnostic and procedural codes with indicating diagnoses consistent with cirrhosis (Table 1) as primary diagnosis were identified. Standardized costs for all billed inpatient services included professional and hospital services for the inpatient stay as well as for time spent in the emergency department or observation preceding admission. Costs retrieved from the National Health Security Office Cost Data Warehouse were created by applying Universal Coverage Scheme reimbursement to professional services, multiplying service-line hospital charges by medical cost report cost to charge ratios, and adjusting for inflation with the gross domestic product implicit price deflator. Disposition at 1 year was determined by a review of electronic health records. For those patients whose medical records did not specify status at 1 year, survival status at 1 year was confirmed by social security number. We excluded elective admission from medical investigations or

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TABLE 1. DIAGNOSES CONSISTENT WITH CIRRHOSIS AS DEFINED BY ICD-10, CLINICAL MODIFICATION

Esophageal varices with bleeding	I85.01
Esophageal varices without bleeding	I85.00
Varices in diseases classified elsewhere with/without bleeding	I85.10, I85.11
Spontaneous bacterial peritonitis	K65.2
Alcoholic cirrhosis	K70.30
Cirrhosis of liver without mention of alcohol	K74.0
Hepatorenal syndrome	K76.7
Hepatic encephalopathy	K72.90, K72.91

scheduled procedures. We identified unique index hospitalizations for adults (ages 18 years or older) who were discharged with diagnoses consistent with cirrhosis as defined by ICD-10, World Health Organization (WHO) version for 2016 codes according to previously validated protocols.[4] Inclusion criteria included patients receiving a diagnosis of cirrhosis following ICD-10 codes (K70.3, K74.0, K74.6, K74.69, K74.3, K74.4, K74.5) with or without certain complications of cirrhosis, such as portal hypertension (K76.6), hepatic encephalopathy (HE; K72.90, K72.91), variceal bleeding (I85.01), hepatocellular carcinoma (HCC; C22.0, C22.7, C22.8), spontaneous bacterial peritonitis (K65.2), and hepatorenal syndrome (HRS; K76.7) as described in Table 1. We tested the validity of the ICD-10, WHO Version for 2016 codes in an administrative database from Phramongkutklao Hospital using a medical-linked system within the hospital database (using 100 random medical records) to identify patients. This set of ICD-10 codes, WHO Version for 2016 identified patients with cirrhosis with high accuracy (sensitivity 92% and specificity 94%). Ascites (R18.8) did not add to the accuracy of diagnosis of cirrhosis. Individuals were excluded from the study if they (1) had elective admission for scheduled therapeutic procedures, such as transarterial chemoembolization for HCC (n = 20,971), (2) died during the initial hospitalization (n = 19,544), or (3) received a liver transplant before or during the study period (n = 0).

The primary outcomes were risks for first hospitalization and 30-day inpatient readmission; the secondary outcomes were cost and status at 1 year. Our predictors consisted of complications of cirrhosis (ascites [ICD-10-WHO R18.8], variceal bleeding [I85.01], HE [K72.90, K72.91], HRS [K76.7], and HCC [C22.0, C22.7, C22.8]) with cause of liver disease (alcoholic liver disease [K70, K70.9], hepatitis C virus [B17.1, B18.2, B19.2], and hepatitis B virus [B16, B18.1, B18.1, B19.1]). Other exposure variables included age, sex, hospital size, and geographic region of the country. Comorbidity and illness severity were controlled using the Charlson comorbidity index[9] after eliminating liver disease and HCC. Time to first readmission was measured at the median (67 days). Primary reasons for readmission were identified using the first listed ICD-10-WHO code for hospitalization. Reasons for readmission were then further grouped more broadly according to the authors' discretion.

Mortality rate was captured from the death certificate database.

STATISTICAL ANALYSIS

Data were summarized as the median (interquartile range) or mean (range) for continuous outcomes or counts and percentages for categorical outcomes. Normal distributions were verified by visual inspection. We used Wilcoxon rank sum tests for continuous data and the chi-square or Fisher exact tests for categorical data to determine differences between groups. Two-tailed *P* values were reported with *P* less than 0.05 considered statistically significant. The C statistic was computed to describes the discriminatory performance of the model using significant univariate variables and important clinical variables, which were then included in the multivariate model.

We first described readmission rates at 30 days, as well as specific subgroups of interest including geographic region, hospital size, and health care delivery system. Next we described the top reasons for readmission based on the ICD-10-WHO code (Table 1) and analyzed data using SPSS Statistics (IBM, Armonk, NY).

Results

PATIENT POPULATION, ADMISSION, AND READMISSION RATES

After applying the inclusion and exclusion criteria, we identified 134,038 unique index admissions.

Overall, most patients were admitted in the north and northeastern regions of Thailand, and 28.3% were admitted to a hospital with more than 500 beds. The demographics, clinical characteristics, and details of each patient's index admission are described in Table 2. In general, 37% of patients had alcoholic cirrhosis and 66% of patients had viral hepatitis (hepatitis B and C). Overall, 54.5% had one complication, 8.6% had two complications, and 2.8% had three or more complications. Of all hospitalizations, 54% involved portal hypertension complications and 28% involved infections. The median age of patients in the index cohort was 54.7 years, and 66.4% were men (n = 15,088). Comparisons of age and geographical features

TABLE 2. CHARACTERISTICS OF THE INDEX HOSPITAL ADMISSION

Characteristics	Overall (n = 134,038)	30-Day Readmission (n = 22,714)	Non-30-Day Readmission (n = 111,324)
Age, mean (SD)	54.20 (13.8)	54.66 (13.3)	54.10 (13.9)
Sex (% male)	92,533 (69.0)	15,088 (66.4)	77,445 (69.6)
Regional Classification			
Northern	26,372 (19.7)	4,543 (20.0)	21,829 (19.6)
Northeastern	45,400 (33.9)	7,025 (30.9)	38,375 (34.5)
Western	10,642 (7.9)	1,896 (8.3)	8,746 (7.9)
Eastern	12,746 (9.5)	2,336 (10.3)	10,410 (9.4)
Central and Bangkok Metropolitan Region	28,456 (21.2)	5,028 (22.1)	23,428 (21.0)
Southern	10,418 (7.8)	1,886 (8.3)	8,532 (7.7)
Health Care Level			
Community hospital	48,225 (36.0)	8,147 (35.9)	40,078 (36.0)
Provincial hospital	47,868 (35.7)	8,087 (35.6)	39,781 (35.7)
Regional hospital	37,940 (28.3)	6,480 (28.5)	31,460 (28.3)
Length of Stay			
1 day	14,718 (11.1)	2,428 (10.8)	12,290 (11.2)
2-4 days	58,013 (43.7)	9,272 (41.2)	48,471 (44.3)
5-13 days	48,096 (36.3)	8,736 (38.9)	39,360 (35.7)
> 13 days	11,775 (8.9)	2,044 (9.1)	9,731 (8.8)
Cost of Hospitalization (US $*), mean (SD)	637.54 (1,223.13)	638.01 (1,163.35)	637.44 (1,234.98)
One-year mortality	52,087 (38.9)	14,433 (63.5)	37,654 (33.8)
Charlson Comorbidity Index			
0-1	108,841 (81.2)	18,135 (79.8)	90,706 (81.5)
2-3	22,888 (17.1)	4,172 (18.4)	18,716 (16.8)
4-5	2,065 (1.5)	368 (1.6)	1,697 (1.5)
6+	244 (0.2)	39 (0.2)	205 (0.2)
Cirrhotic Complication			
Ascites (R18)	11,475 (8.6)	3,323 (14.6)	8,152 (7.3)
Variceal hemorrhage (I850)	8,835 (6.6)	1,408 (6.2)	7,427 (6.7)
Hepatic encephalopathy (K729)	7,519 (5.6)	1,882 (8.3)*	5,637 (5.1)
Hepatorenal syndrome (K767)	595 (0.4)	111 (0.5)	484 (0.4)
HCC (C220)	5,639 (4.2)	1,332 (5.9)	4,307 (3.9)
Underlying Disease			
Alcoholic liver disease (K703)	44,010 (32.8)	6,895 (30.4)	37,115 (33.3)
HIV infection	2,598 (1.9)	370 (1.6)	2,228 (2.0)
Diabetes mellitus	699 (0.5)	119 (0.5)	580 (0.5)
Cholangiocarcinoma	776 (0.6)	75 (0.3)	701 (0.6)

*US $1 = 32.5 baht (referenced December 2013).

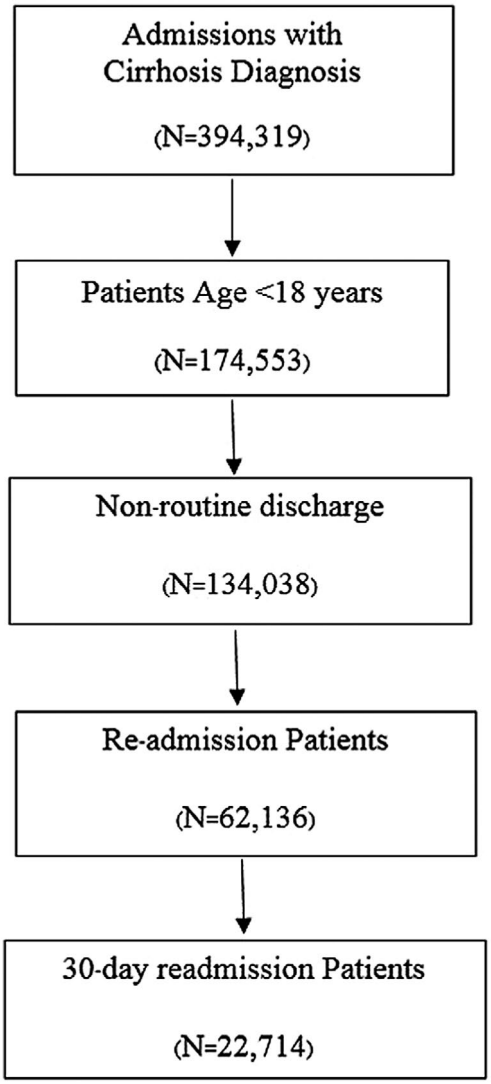

FIG. 1. Inclusions and exclusions.

between patients readmitted within 30 days and patients not readmitted within 30 days did not differ. Comorbidity index, ascites, and HE among patients readmitted within 30 days were significantly higher than the control group. Figure 1 summarizes inclusions and exclusions including nonroutine discharges, in-hospital mortality, and liver transplant before and during index admission.

Patients discharged after index hospitalization for cirrhosis had an even higher rate of early readmission. The median time to readmission was 67 days after being discharged. The observed overall 30-day readmission rate was 17%. Most readmissions were to the same hospital as the index of admission. The 30-day readmission rate at a community hospital (fewer than 120 beds) was 16.9%, 16.9% at an intermediate-level hospital (121-500 beds), and 17.1% at a referral hospital (more than 500 beds). These rates did not tend to vary in clinical detail across the country or among the causes of cirrhosis. Subgroup analysis of health care level revealed that the 30-day readmission rate did not differ, but total readmissions in a community hospital were higher than those in a referral hospital.

REASONS FOR READMISSION AND VARIABLES ASSOCIATED WITH 30-DAY READMISSION

Gastrointestinal hemorrhage was the most common reason for readmission within 30 days and at specific time points at 7, 14, and 30 days. Infection and alcohol-related conditions were the second and third most common reasons for 30-day readmission, respectively. Among the infections, gastrointestinal infection and sepsis were the most common causes of infection. In total, 26 significant variables were associated with 30-day readmission using univariate analysis. Using multivariate analysis adjusted for age, sex, and comorbidity, HCC was a significant readmission predictor (hazard ratio [HR] 1.95; 95% confidence interval [CI]: 1.84, 2.06; $P < 0.001$) followed by human immunodeficiency virus (HIV)-related admission (HR 1.81; 95% CI: 1.51, 2.17; $P < 0.001$) and cholangiocarcinoma (HR 1.64; 95% CI: 1.30, 2.05; $P < 0.001$) in rank order. We developed a model to predict risk of 30-day readmission. However, the model exhibited poor discriminative ability with a C statistic of 0.6. Predictors for 30-day readmission are summarized in Table 3.

COSTS OF HOSPITALIZATION AND READMISSION

Readmitted patients had lower average index hospitalization costs per visit than those of patients without readmission. However, 30-day readmission costs were significantly higher than those of the non-30-day readmission group. Index hospitalization and 30-day readmission costs were significant higher in a referral hospital.

TABLE 3. PREDICTORS FOR 30-DAY READMISSION: UNIVARIATE AND MULTIVARIATE ANALYSIS

	Univariate		Multivariate	
Characteristics	Crude HR (95% CI)	*P* Value	Adjusted HR (95% CI)	*P* Value
Sex (female)	1 (0.97-1.03)	0.938	0.95 (0.92-0.97)	<0.001
Age (year)*	1.008 (1.007-1.009)	<0.001	1.006 (1.005-1.007)	<0.001
Region				
North region	1 (reference)		1 (reference)	
Northeast region	1.003 (0.97-1.04)	0.885	1 (0.96-1.04)	0.960
West region	0.97 (0.92-1.02)	0.250	0.96 (0.91-1.01)	0.106
East region	0.97 (0.92-1.02)	0.176	0.96 (0.91-1.01)	0.086
Central region	0.95 (0.91-0.99)	0.011	0.92 (0.88-0.96)	<0.001
South region	1.02 (0.97-1.08)	0.485	0.99 (0.94-1.05)	0.832
Hospital Level				
Community hospital	1 (reference)		1 (reference)	
Provincial hospital	1.04 (1.01-1.07)	0.022	1.06 (1.03-1.09)	<0.001
Regional hospital	1.01 (0.98-1.04)	0.530	1.04 (1.00-1.07)	0.051
Variables at Index of Admission				
Length of stay*	1.003 (1.002-1.003)	<0.001	1.003 (1.002-1.003)	<0.001
Charlson comorbidity index*	1.17 (1.15-1.18)	<0.001	1.13 (1.11-1.15)	<0.001
HCC	1.93 (1.82-2.04)	<0.001	1.95 (1.84-2.06)	<0.001
HIV-related admission	1.59 (1.33-1.91)	<0.001	1.81 (1.50-2.17)	<0.001
Cholangiocarcinoma	1.64 (1.31-2.05)	<0.001	1.64 (1.30-2.05)	<0.001
Non-liver-related admission	1.28 (1.06-1.55)	0.011	1.32 (1.09-1.59)	0.004
Bacterial sepsis	1.17 (1.09-1.26)	<0.001	1.18 (1.10-1.28)	<0.001
Respiratory tract infection	1.11 (1.03-1.19)	0.006	1.13 (1.04-1.21)	0.002
Gastrointestinal Bleeding				
None	1 (reference)		1 (reference)	
Nonvariceal bleeding	0.88 (0.85-0.91)	<0.001	0.92 (0.89-0.96)	<0.001
Variceal bleeding	0.63 (0.60-0.66)	<0.001	0.68 (0.65-0.72)	<0.001
Complications of Cirrhosis				
SBP	1.38 (1.30-1.46)	<0.001	1.4 (1.32-1.48)	<0.001
Ascites without SBP	1.37 (1.16-1.61)	<0.001	1.37 (1.12-1.67)	0.002
Hepatorenal syndrome	2.28 (1.89-2.76)	<0.001	1.43 (1.21-1.69)	<0.001
Liver failure	1.49 (1.39-1.59)	<0.001	1.51 (1.40-1.61)	<0.001

*Data are represented in continuous variables, for a 1-unit increase in continuous predictor variable (adjusted HR).
Abbreviation: SBP, spontaneous bacterial peritonitis.

OUTCOMES 1 YEAR AFTER HOSPITAL DISCHARGE

Among the 22,714 patients readmitted within 30 days, the 1-year mortality rate was higher than that of those not readmitted (63.5% vs. 33.8%, $P < 0.001$). In all, 4,226 in-hospital deaths occurred during readmission, and 10,197 out-of-hospital deaths or 11,423 total deaths (63.5%) occurred within 1 year after the initial hospital admission. The overall 1-year mortality rate among hospitalized patients was 38.9%. Causes of death were mostly from liver-related mortality and infection.

Discussion

This study focused on hospitalized patients with cirrhosis identified nationwide regarding all-payer parties in the Thai Ministry of Public Health database. Our study demonstrates readmission rates in a nationwide population database. This study discovered six key findings. First, the incidence of 30-day readmission for patients with cirrhosis was 17% and did not differ between community and tertiary care hospitals. This number was higher than a geographically representative study conducted in the United

States.[7] Second, age and male sex comprised risk factors for index admission concerning complications of cirrhosis. Third, the length of stay at the index of admission, comorbidity index, and presence of complications of cirrhosis was significantly higher among patients who were rehospitalized within 30 days after discharge from the index, and the median time for readmission was 67 days. Fourth, the presence of liver cancer, both HCC and cholangiocarcinoma, and HIV infection were the strongest predictors of 30-day readmission. Fifth, costs at index of admission for readmitted patients was lower than those of patients without readmission. However, the total costs were more related to costs of readmission. Finally, we also captured patients who died outside of the hospital, at home, or en route to the hospital and in the emergency department using patient identification number. The 1-year outcome for any patient with cirrhosis was somber, with only 36.5% of patients alive within 1 year after the initial hospital admission.

Our previous study presented a 30-day readmission rate of patients with cirrhosis residing within three states in the Midwest area of the United States (Minnesota, Iowa, and Wisconsin), which was 24.3% of the index cohort.[4] Another study from Volk et al. reported a 30-day readmission rate of 37%. The rates reported from these related studies were higher than that in our study because both studies were conducted at an academic hospital that served as a referral center. However, our research involved a population-based study that captured all readmissions within the health care system. A previous study in the United States, which conducted a weighted analysis of the 2014 Nationwide Readmissions Database, reported a readmission rate of 15%, and the main causes of readmission were complications of cirrhosis.[10] Likewise, our data support that cirrhosis is a major economic burden in the health care system, because after initial admission most patients are readmitted again in the health care system. Most reasons cited for readmission were from complications of cirrhosis.[4,7,11,12] Hospital readmissions frequently occur among patients with poor comorbidity and are associated with liver disease severity. Additionally, the increased Model for End-Stage Liver Disease (MELD) score was associated with readmission in most studies.[5]

Liver disease severity, determined by MELD score, was an important factor associated with readmission. In our study, as in those conducted by others,[4,7,11,12] presenting with a high number of cirrhosis complications was an independent predictor of early hospital readmission. These could be explained by the nature of cirrhosis being a chronic complex disease. Increasing MELD score determines the progressive phase marked by developing many complications from liver dysfunction and portal hypertension. Furthermore, having advanced cirrhosis also increases the risk of developing infections, kidney injury, acute-on-chronic liver failure, and HCC.

Clostridium difficile infections (CDIs) also proved to serve as predictors for early readmission in cirrhosis.[13] The Nationwide Readmissions Database in the United States reports that patients with cirrhosis and CDIs were more likely to be readmitted within 30 days and have higher mortality rates than those without cirrhosis. However, our data do not capture laboratory values for CDIs. Patients with decompensated cirrhosis presented the highest risk for 30-day readmission after CDIs. Recurrent CDIs constituted the major reason for early readmission. Intervention to reduce CDIs and prevent recurrent CDIs should include strategies to prevent readmission.

Most patients were readmitted for a liver cirrhosis–related reason in our study, similar to findings in other studies.[4,7,11,12] Modifiable predictors of readmission previously reported include HE, ascites, and other complications of cirrhosis. We also found that HIV-related cases and cholangiocarcinoma predicted 30-day readmission. This could be explained by the high incidence of HIV and cholangiocarcinoma cases related to cirrhosis in Thailand.[14,15] Strategies to reduce hospital readmission in cirrhosis should target high-risk groups such as individuals with several significant comorbidities, like decompensated cirrhosis liver cancer and HIV-positive status.

Several interventions were proposed to reduce hospital readmission in cirrhosis. We developed a model to predict 30-day readmission. However, the model indicated only moderate discriminative ability, as in our previous study,[4] because readmission is complex due to cultural diversity and the ability to access health services. Readmission risk score may highlight the need for targeted interventions to decrease rates of readmission within high-risk populations.[16] However, some factors are not easily manageable due to their complexity such as culture, socioeconomic status, and health insurance.

Our study had some limitations inherent to research involving administrative database analysis. First, this study relied on ICD10-WHO codes to establish a diagnosis of cirrhosis. Theoretically, miscoding or error in the code-assignment process could have led to misclassification bias. Second, our data from the National Health Security Office did not capture laboratory values and medications. Therefore, we could not analyze their effect on 30-day readmission, especially variables such as MELD or Child-Turcotte-Pugh scores, which prevented the severity of cirrhosis from being assessed.

In conclusion, this study used a nationwide database to capture the burden of readmission involving cirrhosis in a health economic perspective, outside of the United States. We determined that the 30-day, all-cause readmission rate among patients with decompensated cirrhosis was 17%, and most readmissions were from decompensated-related causes. Comorbidities such as liver cancer and HIV also predicted the risk for 30-day readmission among patients with cirrhosis. Despite the inherent limitations of administrative databases, the results of this study could have several clinical implications, especially the potential to help health care policy stakeholders to target high-risk patients. Future studies should focus on interventions to target patients at high risk for readmission and aim to decrease 30-day readmission rates.

Ethical Consideration

This study was approved by the Gastroenterological Association of Thailand in collaboration with the National Health Security Office of Thailand. All data used in this study were de-identified and released for research purposes. The research protocol was approved by the Institutional Review Board, Faculty of Tropical Medicine, Mahidol University (FTM ECF-019-04), and was carried out according to the Good Clinical Practice Guideline without obtaining informed consent.

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